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Examiner: Ganapathy Krishnan
Group No. 1623

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Appellants: Yat Sun Or
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Docket No. 4014.1074 US
Expedited Procedure under 37 C.F.R. 1.116
Examining Group 1623

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	:	10/763,377	Confirmation No. 7571	
Appellant	:	Yat Sun Or		
Filed	:	January 23, 2004		
TC/A.U.	:	1623	Examiner :	Ganapathy Krishnan
Docket No.	:	4014.1074 US		

For: Bridged Macrocyclic Compounds and Processes for the Preparation Thereof

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APPEAL BRIEF

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Commissioner for Patents
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Sir:

This Replacement Brief is being filed pursuant to 37 CFR 41.37 and the Notification of Non-Compliant Brief dated July 16, 2007. The required sections under 37 CFR §41.37 are set forth below under separate headings.

(i) *Real party in interest*

The real party of interest in this appeal is Enanta Pharmaceuticals Inc. by virtue of Assignment recorded on April 14, 2004 at Reel 014517 and Frame 0053.

(ii) *Related appeals and interferences*

There are no related appeals or interferences.

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(iii) *Status of claims*

Claims 1-12 and 15 are pending, finally rejected. Claim 15 has been canceled and claims 1-12 are appealed.

(iv) *Status of the Amendments*

No amendment after final rejection has been filed.

(v) *Summary of claimed subject matter*

The invention relates to a process of bridging a macrocylic system with a bifunctional bridging component characterized by its ability to form a π-allyl metal complex. Independent Claim 1 is directed to a process comprising the step of reacting a macrocyclic compound characterized by at least two nucleophilic moieties with a bifunctional bridging component characterized by its ability to form a π-allyl metal complex in the presence of catalyst thereby achieving a bridged macrocyclic product. See page 22, lines 22-30. Dependent Claims 2-12 are directed to a macrolide as the macrocyclic system. See pages 3-7.

(vi) *Grounds of rejection to be reviewed on appeal*

There are two grounds of rejection (issues) on appeal. The first issue on appeal is whether the specification enables the full scope of claim 1 under 35 U.S.C §112, first paragraph. The second issue is whether the Examiner has established a case of obviousness of claims 1-12 over Or et al, PCT Application WO99/21864 ("WO '864").

(vii) *Argument*

Rejection under 35 USC 112, first paragraph

Claim1

In the Final Office Action, the Examiner has maintained the rejection of independent claim 1 under 35 U.S.C 112, first paragraph, asserting that while the specification is enabling for macrolides, it does not reasonably provide enablement for a process using any macrocyclic compound. The Examiner presented the structure

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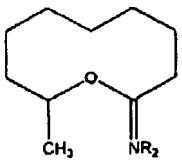

, and stated that the oxygen atom and the NR_2 groups that bear electron pair are nucleophiles. The Examiner has provided no evidence in support of this allegation. The Examiner further asserted that such macrocycle cannot form a bridge as instantly claimed. The Examiner concludes that since at least one macrocyclic compound could be envisioned that would not bridge, the specification is not enabling for its scope.

According to MPEP §2164.08(b), the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984).

It is undisputed that the structure presented by the Examiner cannot form a bridge. However, a person having skill in the art would recognize that the oxygen atom in this structure is not nucleophilic. A nucleophile requires more than the mere presence of an oxygen. Even if one were to consider it to be a nucleophile, the ring oxygen atom as presented by the Examiner would be positive if a bridge was to form. Such a trivalent positive oxygen is unstable and would not be consider standard chemistry. Thus, it is clear that a person of ordinary skill in the art should be able to immediately recognize and predict many macrocycles that can or cannot undergo bridge formation before actually carrying out the process as instantly claimed. Indeed, in this case, the Examiner selected this compound because he is confident it cannot undergo a bridging reaction. The identification of what is apparently an obvious compound that will fail in the reaction does not prove that the rejection is proper. Further, in cases where it is hard to predict the bridge formation, it would only be routine experimentation for one of ordinary skill in the art to carry out the process as instantly claimed and determine which macrocycles would be inoperative or operative. The Appellant submits that the process as instantly claimed has been exemplified on a variety of complex macrolide structures and the specification provides ample directions and guidance to carry out the process. A skilled person in the art

can easily determine which embodiments would be inoperative or operative following the instant claimed process without undue experimentation.

Furthermore, the presence of one or more "failed" experiments does not necessarily render a claim nonenabled. Indeed, in *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988), five out of nine embodiments made were inoperative. Yet the USPTO determined that the claims were enabling because the specification provides a considerable amount of direction and guidance on how to practice the claimed invention and presented working examples, that all of the methods needed to test the compounds were well known, and that there was a high level of skill in the art at the time the application was filed. *Wands* does not require that the outcome of each experiment be successful or predicted a priori. The Appellant submits that the teaching in the present specification establishes that it does not take undue experimentation to be successful.

Rejection under 35 USC 103(a)

Claims 1-12

The Examiner has maintained the rejection under 35 U.S.C 103(a) of independent claims 1-12 as being obvious over PCT Application WO99/21864 ("WO '864").

The rejection notes that WO '864 teaches a process for making a bridged macrocyclic compound with the bridging components H_2N-$(CH_2)_m$-A-B-D-X and $(CH_2)_2$-C=CH_2. The Examiner asserts that the macrocyclic compounds disclosed in WO'864 has at least two nucleophilic groups and are structurally very close to the macrocyclic compounds used for the said bridging in the instant process. The Examiner further states that the second bridging component with the double bond forms a pi-allyl complex with a metal. The difference between the claimed and prior art processes is in that the prior art uses two bridging components to achieve a bridge while the claimed invention uses a single bridging component. While the Examiner recognizes that the presently claimed process discloses that bridging can be achieved in fewer steps compared to the process disclosed in WO '864, he asserts that the fact that it can be achieved in fewer steps is also the motivation for carrying out the process as instantly claimed. During the telephonic interview on March 8, 2007, the Examiner further clarified that it would have been obvious

to couple the bridging components described in WO '864 into one component first before bridging it to the macrocyclic compound.

The overall process disclosed in WO '864 generally provides different bridged compounds than presently claimed. The process that the Examiner relied upon for the rejection is the process using two bridging components H_2N-$(CH_2)_m$-A-B-D-X and X-$(CH_2)_n$-C=CH_2. The process disclosed therein required that the X-$(CH_2)_n$-C=CH_2 component be added to the macrocycle first as shown in schemes 2-4. The second component is then added to the same macrocycle and the two ends of the components are then tied together *via* a Heck type reaction when X is a leaving group or olefin metathesis when X is an olefin. The assertion by the Examiner that the individual components can be coupled first before bridge formation and hence is obvious to the presently claimed invention is erroneous. Firstly, the allegation is not supported by evidence. Secondly, taking the two bridging components and then coupling them prior to bridging does not in fact reduce the number of steps. Thirdly, the process suggested by the Examiner would be expected to reduce efficiency based on the possible side reactions. The Examiner recognized that the coupling reaction of the two components described in WO '864 will give a complex reaction, however he asserted that the desirable coupled product will also form and thus makes obvious to the present invention. It is not clear how a process that would be expected to lower the overall yield resulting from complex mixtures can make obvious the claimed process, which resulted in a very high yield. It is believed that the Examiner has failed to consider all of the factual inquiries set forth in *Graham* v. *John Deere Co.* when determining obviousness, particularly objective evidence that is present in the application. The present invention clearly describes a new and improved process of bridge formation on a macrocycle that is nonobvious from WO '864.

To further support the rejection, the Examiner cited two cases, *In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347 (Fed. Cir. 1992), and asserted that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. The Appellant completely agrees with the Examiner's statement. However, it is not clear how this saves the present rejection. The

Examiner has found the motivation to make a change. However, the Examiner has failed to articulate the teachings or suggestions in the art as to how one would make the generally desirable change. This is clearly improper.

Determination of obviousness under §103 is a highly fact-specific. It requires one to weigh the specific differences between the claimed invention with all its limitations and the prior art, see *In re Ochiai*, 71 F.3d 1565 (Fed. Cir. 1995). In *In re Ochiai*, the Federal Circuit found that both the Examiner and the Board erred in determining obviousness in that they applied a *per se* rule of obviousness instead of conducting a fact intensive inquiry as required by patent law for determining obviousness because they employed an incorrect general obviousness rule that states that a process claim is obvious if prior art references disclose the same general process using similar starting materials. Even if the bridging component of the claimed process has a common property (the ability to form a pi-allyl bond) with a starting material disclosed by Or *et a.l*, the process is quite different.

To further support the Appellant's point of view, both *In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347 (Fed. Cir. 1992), cited by the Examiner, were reversed by the Federal Circuit with a conclusion that the PTO had not made a *prima facie* case of obviousness. In *In re Fine*, the Federal Circuit found that the PTO points to nothing in the cited references, either alone or in combination, suggesting or teaching of Fine's invention. The court further states:

> "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher"

As for *In re Jones*, the Federal Circuit found no evidence, other than the PTO's speculation that one of ordinary skill in the herbicidal art would have been motivated to make the modification of the prior art salts necessary to arrive at the claimed 2-(2'-aminoethoxy)ethanol salt. Just as in the present invention, the Examiner speculates that one of ordinary skill in the art would have been motivated to modify the process of Or *et al.* to arrive at the instantly claimed process because the claimed process is achieved with

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fewer steps. However, there is no evidence present in Or *et al.* disclosure that the modification necessary to "reduce" the number of steps was known.

(viii) *Claims appendix*

See attached

(ix) *Evidence appendix*

None

(x) *Related Proceedings Appendix*

None

Summary

Appellant asks that the rejections under 35 U.S.C 112, first paragraph and the rejection of obviousness under 35 U.S.C 103 be reversed.

Respectfully submitted,

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By _____

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(viii) *Claims appendix*

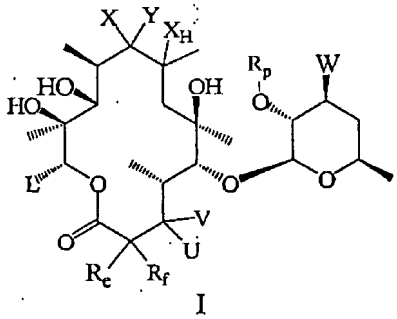
1. (Previously presented) A process comprising the step of reacting a macrocyclic compound characterized by at least two nucleophilic moieties with a bifunctional bridging component characterized by its ability to form π-allyl metal complex in the presence of catalyst thereby achieving a bridged macrocyclic product.

2. (Original) The process of claim 1, wherein the macrocyclic compound is a macrolide antibiotic.

3. (Original) The process of claim 1, wherein the macrocyclic compound is an erythromycin derivative.

4. (Original) The process of claim 3, wherein the erythromycin derivative is azithromycin, desmethyl azithromycin, roxithromycin, clarithromycin, telithromycin, or cethromycin.

5. (Original) The process of claim 1, wherein the macrocyclic compound is selected from:



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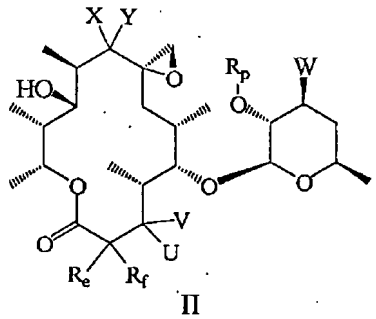

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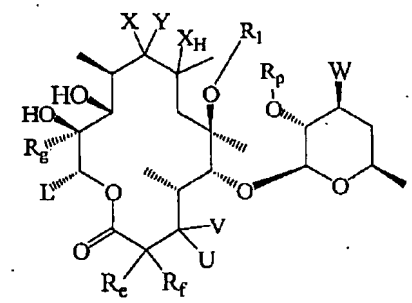

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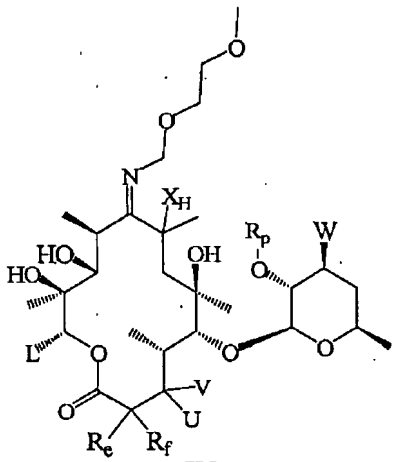

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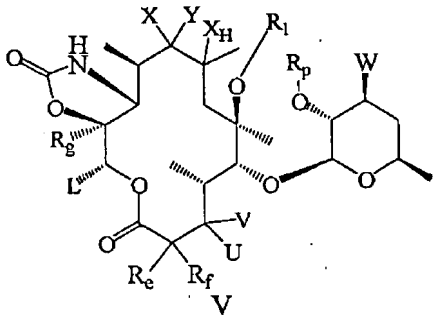

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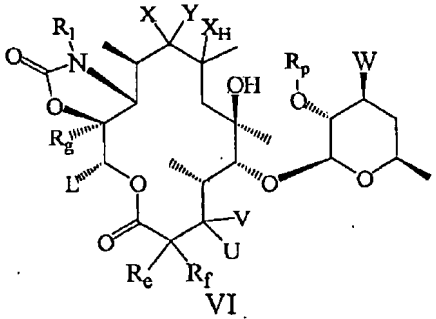

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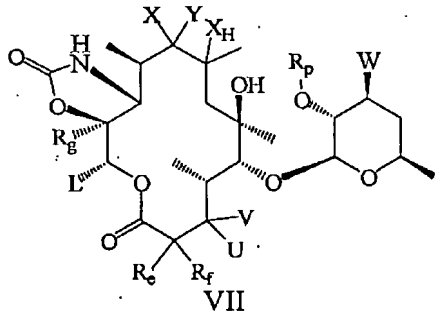

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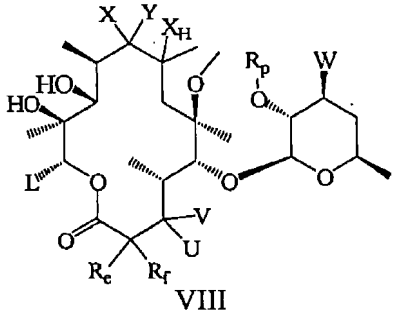

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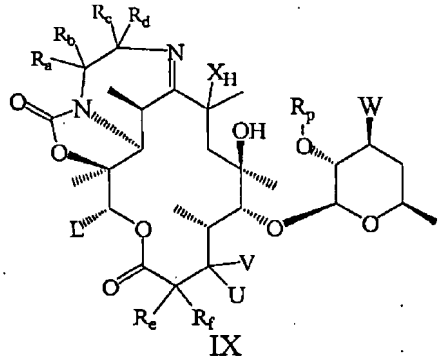

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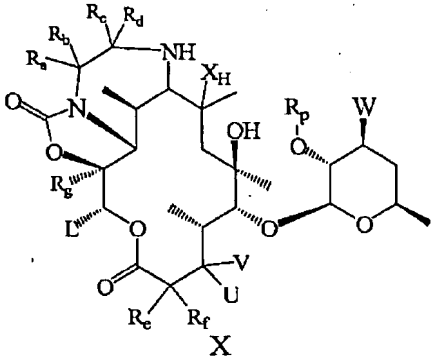

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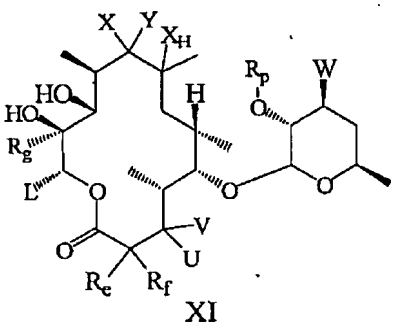

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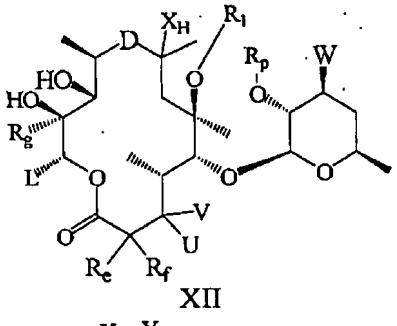

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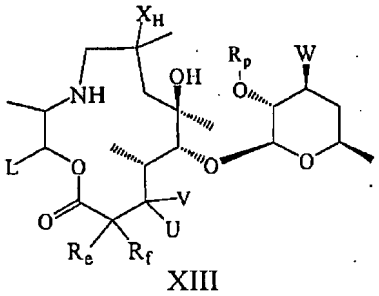

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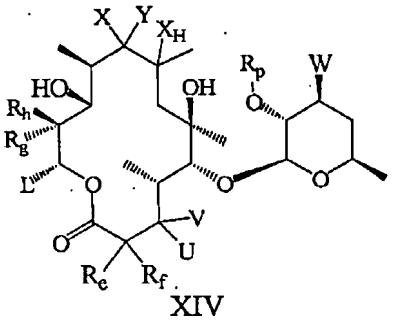


XIV

wherein

D is selected from $-NHCH_2-$, $-NHCHR_1-$, $-NHCR_3R_4-$, $-NR_1CH_2-$, -NHC(O)-, $-NR_1C(O)-$, -NHC(S)-, or $-NR_1C(S)-$;

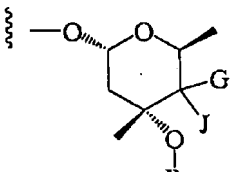
Each R_1 is independently selected from hydrogen, deuterium, a substituted or unsubstituted, saturated or unsaturated aliphatic group, a substituted or unsubstituted, saturated or unsaturated alicyclic group, a substituted or unsubstituted aromatic group, a substituted or unsubstituted heteroaromatic group, saturated or unsaturated heterocyclic group;

R_3 and R_4 is independently selected from the group consisting of hydrogen, acyl, a substituted or unsubstituted, saturated or unsaturated aliphatic group, a substituted or unsubstituted, saturated or unsaturated alicyclic group, a substituted or unsubstituted aromatic group, a substituted or unsubstituted heteroaromatic group, saturated or unsaturated heterocyclic group; or can be taken together with the nitrogen atom to which they are attached to form a substituted or unsubstituted heterocyclic or heteroaromatic ring;

L is selected from hydrogen, a substituted or unsubstituted, saturated or unsaturated aliphatic group, a substituted or unsubstituted, saturated or unsaturated alicyclic group, a

substituted or unsubstituted aromatic group, a substituted or unsubstituted heteroaromatic group, or a substituted or unsubstituted heterocyclic group;

one of U or V is hydrogen and the other is independently selected from the group



consisting of: R_1, OR_1, $OC(O)R_1$, $OC(O)NR_3R_4$, $S(O)_nR_1$, or other carbohydrate or sugar moiety;

or U and V, taken together with the carbon atom to which they are attached, are C=O;

or UV and R_eR_f, taken together with the carbon atoms to which they are attached, are $-C(R_1)=CH-$;

one of J or G is hydrogen and the other is selected from: R_1, OR_1, or NR_3R_4;

or J and G, taken together with the carbon atom to which they are attached, are selected from: C=O, $C=NR_1$, $C=NOR_1$, $C=NO(CH_2)_mR_1$, $C=NNHR_1$, $C=NNHCOR_1$, $C=NNHCONR_3R_4$, $C=NNHS(O)_nR_1$, or C=N-N=CHR_1;

R_a, R_b, R_c, and R_d are independently selected from $-R_1$, $-OR_1$, $-S(O)_nR_1$, $-C(O)OR_1$, $-OC(O)R_1$, $-OC(O)OR_1$, $-C(O)R_1$, $-C(O)NH-R_1$, $-NHC(O)-R_1$, $-N(R_3)(R_4)$, $-NHC(O)-OR_1$, $-NHC(O)NH-R_1$, or $-OC(O)NH-R_1$;

or R_a and R_b, R_a and R_c, R_a and R_d, R_b and R_c, R_b and R_d, or R_c and R_d, taken together with the carbon atom or atoms to which they are attached, are selected from substituted or unsubstituted alicyclic or substituted or unsubstituted heterocyclic;

one of R_e and R_f is selected from hydrogen or methyl, and the other is independently selected from halogen, deuterium, or R_1;

R_h is hydroxy;

R_g is selected from hydrogen, a substituted or unsubstituted, saturated or unsaturated aliphatic group, a substituted or unsubstituted, saturated or unsaturated alicyclic group, a substituted or unsubstituted aromatic group, a substituted or unsubstituted heteroaromatic group, or a substituted or unsubstituted heterocyclic group;

or R_g and R_h, taken together with the carbon atom to which they are attached, are selected from an epoxide, a carbonyl, a substituted or unsubstituted olefin, a substituted or unsubstituted alicyclic, a substituted or unsubstituted heterocyclic;

W is NR_3R_4;

one of X and Y is hydrogen, substituted or unsubstituted aliphatic, and the other is independently selected from: hydroxy, -SH, $-NH_2$, or $-NR_1H$;

or X and Y, taken together with the carbon atom to which they are attached, are selected from: C=O, $C=NR_1$, $C=NOR_1$, $C=NO(CH_2)_mR_1$, $C=NNHR_1$, $C=NNHCOR_1$, $C=NNHCONR_3R_4$, $C=NNHS(O)_nR_1$, or C=N-N=CHR_1;

R_p is selected from hydrogen, acyl, silane, or a hydroxy protecting group;

X_H is selected from hydrogen or halogen;

m is an integer; and

n is 0, 1, or 2.

6. (Previously presented) The process of claim 5, wherein, for the macrocylic compound, L is ethyl.

7. (Previously presented) The process of claim 5, wherein, for the macrocylic compound, one of X and Y is hydrogen and the other is selected from hydroxy or amino.

8. (Previously presented) The process of claim 5, wherein, for the macrocylic compound, X and Y, taken together with the carbon atom to which they are attached, are selected from the group consisting of: C=O, C=NH, C=N-OH, or $C=N-NH_2$.

9. (Previously presented) The process of claim 5, wherein, for the macrocylic compound, R_g is methyl.

10. (Previously presented) The process of claim 5, wherein, for the macrocylic compound, R_e is hydrogen and R_f is selected from methyl, allyl, or propargyl.

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11. (Previously presented) The process of claim 5, wherein, for the macrocyclic compound, one of U and V is hydrogen and the other is selected from –OH or -O-cladinose.

12. (Previously presented) The process of claim 5, wherein, for the macrocylic compound, U and V, taken together with the carbon atom to which they are attached, are C=O.

13. (Canceled)

14. (Canceled)

15. (Canceled)